Virology 277, 1–5 (2000)
doi:10.1006/viro.2000.0624, available online at http://www.idealibrary.com on IDEAL®

MINIREVIEW

Epstein–Barr Virus Entry into Cells

Peter Speck, Keith M. Haan, and Richard Longnecker[1]

Microbiology–Immunology Department, Northwestern University Medical School, 303 East Chicago Avenue, Chicago, Illinois 60611

Received July 26, 2000; returned to author for revision August 15, 2000; accepted September 1, 2000

Epstein–Barr virus (EBV), a gamma herpesvirus persisting in B cells of most adults, is the prototypic human tumor virus. Persistent infection associates with malignancies and proliferative syndromes mainly affecting lymphoid and epithelial tissues (Rickinson and Kieff, 1996). EBV was discovered after Denis Burkitt, working in Africa in the 1950s, proposed that an infectious agent was involved in the etiology of a childhood tumor, now known as Burkitt's lymphoma (Burkitt, 1962). Herpesvirus-like particles were subsequently observed on electron microscopic examination of cell lines derived from these tumors (Epstein *et al.,* 1964). In lymphoid tissues EBV-associated tumors include Burkitt's lymphoma, Hodgkin's disease, and certain adult T-cell lymphomas. EBV infection associates with the epithelial disorders nasopharyngeal carcinoma, gastric carcinoma, and oral hairy leukoplakia (Osato and Imai, 1996; Rickinson and Kieff, 1996), the latter occurring in immunocompromised patients. In this group the presence of EBV also associates with lymphoproliferative diseases and with leiomyosarcoma, a tumor of smooth muscle origin. EBV genomes and gene expression have been detected in breast cancers (Bonnet *et al.,* 1999; Labrecque *et al.,* 1995). Evidence for this association, e.g., detection of viral genomes in each malignant cell within a tumor, has been reviewed recently by Cohen (2000). As exhibited by the range of pathology described above, EBV clearly gains entry to a variety of cell types, notably B cells and epithelial cells. Studies of EBV biology have been facilitated by construction of viruses containing drug resistance markers, for example that described by Shimizu *et al.* (1996). A recent enhancement of this approach is development of viruses carrying reporter genes, such as that designated EBfaV–GFP (Speck *et al.,* 1999; Speck and Longnecker, 1999), which bears the gene for enhanced green fluorescent protein (EGFP) and produces infectious virus in high titer. Use of this reagent enables the ready visualization and enumeration of infected cells. The strategies EBV has evolved to enter its various target cells are complex and incompletely understood. However, evidence is accumulating that entry of EBV, like many other viruses, involves interactions between several viral glycoproteins and multiple cellular entry mediators.

EBV readily infects human B cells *in vitro,* with initial attachment mediated by binding (Fig. 1) of the EBV major outer envelope glycoprotein, gp350/220, with cellular CD21 (Nemerow *et al.,* 1985; reviewed in Kieff, 1996). Induction of high-level expression of CD21 on normally uninfectable cells such as mouse L cells, human T or erythroleukemia cells, or transformed epithelial cells leads to viral adsorption and inefficient infection (Ahearn *et al.,* 1988; Koizumi *et al.,* 1992; Li *et al.,* 1992; Paterson *et al.,* 1995). From this it has been inferred that the specific role of CD21 in EBV infection is to capture virions at the cell surface. The level of CD21 expression required to bind virions is not known. However, BJAB cells, first shown to be infectable in 1975 (Clements *et al.,* 1975), and which express relatively low levels of CD21 compared to other lymphoblastoid cell lines (Speck and Longnecker, 1999), are readily infectable. As with other herpesviruses, such as herpes simplex, additional molecules are necessary and required for postbinding events such as fusion of virus and cell membranes and virus internalization. Table 1 lists EBV glycoproteins involved in viral entry.

Postbinding events in EBV infection involve a complex of at least three additional EBV glycoproteins: gH, gL, and gp42 (Fig. 1). gH and its homologs are involved in entry of HSV and other herpesviruses (Forrester *et al.,* 1992; Fuller *et al.,* 1989; Gompels and Minson, 1986; Haddad and Hutt-Fletcher, 1989; Miller and Hutt-Fletcher, 1988; Peeters *et al.,* 1992). The EBV gH homolog is designated gp85, product of the BXLF2 gene (Heineman *et al.,* 1988; Oba and Hutt-Fletcher, 1988). As with other herpesviruses, gH associates with an accessory protein,

[1] To whom correspondence and reprint requests should be addressed. E-mail: r-longnecker@nwu.edu.

0042-6822/00 $35.00

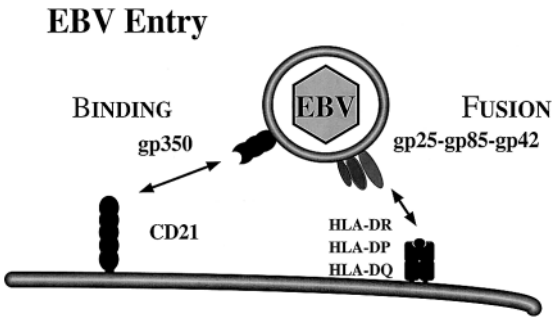

FIG. 1. Epstein–Barr virus infection of B cells. Viral entry into B cells involves the interaction of multiple viral and cellular molecules. The initial attachment of virus to cell is mediated by viral gp350 binding cellular CD21. Postbinding events, mediating internalization of the virus, are known to include interaction between the viral gp25/gp/85/gp42 complex and MHC class II molecules (HLA-DR, -DP, or -DQ) on the cell surface. In contrast, for epithelial cell infection the gH/gL complex does not require gp42 and interacts with a ligand of unknown identity, and gH appears to also have a role in attachment.

a gL homolog designated gp25, product of the BKRF2 ORF (Yaswen *et al.,* 1993). gp85 requires gp25 for its correct folding, transport, and function within the infected cell (Forghani *et al.,* 1994; Hutchinson *et al.,* 1992; Kaye *et al.,* 1992; Liu *et al.,* 1993; Roop *et al.,* 1993; Spaete *et al.,* 1993). Antibodies to gp85 inhibit fusion but not attachment of EBV to B cells (Miller and Hutt-Fletcher, 1988). Virosomes made from EBV proteins bind and fuse with CD21-positive cells; however, without the gH–gL complex they bind but do not fuse (Haddad and Hutt-Fletcher, 1989). In EBV the gp25/gp85 complex associates with the additional glycoprotein gp42, product of the BZLF2 gene (Li *et al.,* 1995). An antibody to the BZLF2 product inhibits infection of B cells but not epithelial cells (Li *et al.,* 1995), implying a role for gp42 in entry of B cells only. The role of gp42 in B cell infection is in penetration of cells rather than attachment, as shown by the finding that EBV lacking gp42 binds B cells normally but cannot penetrate (Wang and Hutt-Fletcher, 1998). Hutt-Fletcher and colleagues showed that MHC molecule HLA-DR is a ligand for gp42 and functions as EBV coreceptor in infection of B cells, confirming an early report of HLA-DR participation in this process (Reisert *et al.,* 1985).

Other molecules are capable of participation in EBV entry (Fig. 1). Haan and colleagues demonstrated that transient expression of HLA-DP or HLA-DQ on CD21-positive, MHC class II-deleted lymphoblastoid cells renders them infectable, showing that these MHC class II isotypes also function as EBV entry mediators (Haan *et al.,* 2000). While it appears that all HLA-DR and -DP molecules function as coreceptors, only -DQ molecules encoding a glutamic acid residue at amino acid 46 of the mature β chain are able to mediate entry (Haan and Longnecker, 2000). This finding is consistent with the groove between the β1 and β2 domains of the HLA molecule being important for gp42 binding and also raises the possibility that EBV-related sequelae might be related to HLA haplotype. The possibility that B cells possess other EBV entry mediators is suggested by the observation that B cells from bare lymphocyte syndrome patients, which in some cases appear to completely lack expression of HLA-DR, -DP, or -DQ, have been infected with and transformed by EBV. It is not known whether the initial binding of EBV to B cells can be mediated by molecules other than CD21. In our hands transient expression of HLA-DR on mouse B cells does not render them infectable, showing that infection is not mediated by HLA-DR alone (data not shown).

The mechanisms underlying EBV infection of epithelial cells remain unclear, in part because an overwhelming majority of epithelial cell lines are refractory to EBV infection *in vitro.* Several routes for direct infection of EBV virions into epithelial cells have been reported, without a common theme emerging. Nonetheless, mechanisms of viral entry into these cell types show a clear divergence from the mechanisms employed in B cell entry. Yoshiyama and colleagues, using EBV bearing a drug resistance gene, describe EBV infection of CD21-negative gastric epithelial cells as shown by derivation of drug-resistant cell colonies (Yoshiyama *et al.,* 1997). While this result implies a CD21-independent infection route, it is possible that very low level expression of CD21 may suffice to permit EBV entry. Fingeroth and colleagues using an epithelial cell line, 293, which expresses low levels of CD21, have shown CD21-dependent infection of

TABLE 1

EBV Glycoproteins Participating in Attachment and Entry

EBV gene	HSV protein[a]	EBV protein	Known or proposed function
BKRF2	gL	gp25	Complexes with gp42 and gp85[c]
BXLF2	gH	gp85	Complexes with gp42 and gp25[c]
BZLF2	gD[b]	gp42	Complexes with gp25 and gp85,[c] binds HLA class II
BALF4	gB	gp110	Virus maturation
BLLF1	gC[b]	gp350/220	Initial attachment by virion binding to CD21

[a] The herpes simplex virus (HSV) glycoproteins which share sequence homology and/or functional homology with EBV glycoproteins.
[b] Although having no sequence homology with EBV glycoproteins, these HSV glycoproteins may serve as functional homologues.
[c] May serve as fusion complex for EBV B cell entry. Epithelial cell entry does not require gp42 and may require a fusion complex lacking gp42.

these cells by the derivation of drug-resistant colonies, supporting the view that low level surface CD21 expression can enable EBV infection of epithelial cells (Fingeroth *et al.,* 1999). Epithelial cells stably transfected to express CD21 at high levels efficiently bind EBV and undergo a transient infection (Li *et al.,* 1992). Recently Hutt-Fletcher and colleagues reported that gH-deleted EBV binds B cells normally but is impaired in attachment to CD21-negative epithelial cells, implying existence of a gH ligand on epithelial cells and a role for gH in attachment and entry of these cells (Molesworth *et al.,* 2000). gp42 is dispensable for infecting cells of the CD21-expressing epithelial line SVKCR2, yet soluble gp42 inhibits this infection and B cell infection, prompting a model of EBV virions forming two types of gH–gL complex, one including gp42 and the other not, with the two forms having mutually exclusive abilities to mediate infection of B cells or epithelial cells (Wang *et al.,* 1998). A possible role for EBV glycoprotein gp150 in epithelial infection is suggested by the observation that recombinant EBV lacking gp150 infects B cells normally but is enhanced in its ability to infect SVKCR2 cells (Borza and Hutt-Fletcher, 1998).

An alternative entry route into epithelial cells has been demonstrated by Sixbey and colleagues who have shown that certain epithelial cells expressing the IgA receptor can internalize EBV, if bound to polymeric IgA (pIgA) (Sixbey and Yao, 1992). In studies using a polarized epithelial cell system, the EBV–pIgA complex enters the basolateral cell surface and is modified and secreted from the opposite (apical) surface of the cell (Gan *et al.,* 1997). Some individuals who have been exposed to EBV express IgA antibodies to EBV-associated antigens in their serum, so in these individuals infection of epithelial cells could potentially occur by this IgA-mediated mechanism. Recent work with this system shows that in polarized MDCK epithelial cells stably expressing CD21, viral uptake is higher on apical than on basolateral surfaces, despite CD21 expression predominating basolaterally, implying that other cell surface molecules may participate in the virus–cell interaction (Chodosh *et al.,* 2000).

Cell-to-cell contact has been described as an efficient means of EBV entry into epithelial cells. Imai and colleagues working with a diverse range of epithelial cell lines derived from gastric and colon adenocarcinoma and hepatocellular, laryngeal, lung squamous cell, and renal cell carcinomas, found that cocultivation of these cells with lymphoblastoid (EBV-bearing) cells leads to EBV infection of the epithelial cells (Imai *et al.,* 1998). Chang and colleagues confirmed this result using nasopharyngeal carcinoma cells, also finding that efficient infection occurs independently of CD21, that cell-to-cell contact is a requirement for the infection, and that cell-to-cell infection could be further enhanced by inducing expression of CD21 (Chang *et al.,* 1999). Recently in this laboratory we have used lymphoblastoid cell lines established by and bearing EGFP-expressing EBV to show, by transfer of EGFP to epithelial cells cocultivated with EGFP-expressing cell lines, that cell-to-cell spread of EBV occurs to breast epithelial cells (Speck and Longnecker, 2000). This finding extends the range of cell types infected by cell-to-cell spread and reinforces the view that EBV may be involved in breast cancer development, as the viral genome and gene products have been detected in these cancers (Bonnet *et al.,* 1999; Labrecque *et al.,* 1995).

There is a paucity of information regarding the mechanisms underlying cell-to-cell spread of virus, and the identity of virally encoded or cellular molecules participating in the process is not known. Cell-to-cell spread of EBV into the epithelium may be of particular clinical relevance as the cell types infected, which include gastric, nasopharyngeal, and breast epithelium, are among those in which EBV has been implicated in tumor development.

Recent findings reveal that, like other herpesviruses such as herpes simplex virus (Spear *et al.,* 2000), EBV has evolved to utilize multiple entry receptors on the cell surface and to enter cells by multiple mechanisms, involving direct virus–cell entry and cell-to-cell spread of virus. Much of the biology of EBV entry into susceptible cells remains obscure. Areas likely to be focused on in the future could include (i) identification of other EBV entry mediators; (ii) elucidation at the molecular level, such as by X-ray crystallography, of interactions between viral and cellular molecules participating in the attachment, fusion, and entry of EBV; and (iii) study within the infected cells of signaling triggered by events at the cell membrane. In addition, despite the clear implication of EBV in certain T cell tumors, there is very little knowledge regarding EBV infection of T cells. Further research to address these issues will provide new insight into the tropism and pathogenesis of a significant human tumor virus.

ACKNOWLEDGMENTS

R.L. is supported by Public Health Service Grants CA62234 and CA73507 from the National Cancer Institute and DE13127 from the National Institute of Dental and Craniofacial Research. R.L. is a Scholar of the Leukemia Society of America. K.M.H. is supported by the training program in the Cellular and Molecular Basis of Disease (T32 GM08061) of the National Institutes of Health. We appreciate the advice and comments of Dr. P. G. Spear.

REFERENCES

Ahearn, J. M., Hayward, S. D., Hickey, J. C., and Fearon, D. T. (1988). Epstein–Barr virus (EBV) infection of murine L cells expressing recombinant human EBV/C3d receptor. *Proc. Natl. Acad. Sci. USA* **85**(23), 9307–9311.

Bonnet, M., Guinebretiere, J., Kremmer, E., Grunewald, V., Benhamou, E., Contesso, G., and Joab, I. (1999). Detection of Epstein–Barr virus in invasive breast cancers. *J. Natl. Cancer Inst.* **91**(16), 1376–1381.

Borza, C. M., and Hutt-Fletcher, L. M. (1998). Epstein–Barr virus recombinant lacking expression of glycoprotein gp150 infects B cells normally but is enhanced for infection of epithelial cells. *J. Virol.* **72**(9), 7577–7582.

Burkitt, D. (1962). A children's cancer dependent on climatic factors. *Nature* **194,** 232–234.

Chang, Y., Tung, C., Huang, Y., Lu, J., Chen, J., and Tsai, C. (1999). Requirement for cell-to-cell contact in Epstein–Barr virus infection of nasopharyngeal carcinoma cells and keratinocytes. *J. Virol.* **73**(10), 8857–8866.

Chodosh, J., Gan, Y.-J., Holder, V. P., and Sixbey, J. W. (2000). Patterned entry and egress by Epstein–Barr virus in polarized CR2-positive epithelial cells. *Virology* **266,** 387–396.

Clements, G. B., Klein, G., and Povey, S. (1975). Production by EBV infection of an EBNA-positive subline from an EBNA-negative human lymphoma cell line without detectable EBV DNA. *Int. J. Cancer* **16**(1), 125–133.

Cohen, J. I. (2000). Epstein–Barr virus infection. *N. Engl. J. Med.* **343**(7), 481–492.

Epstein, M. A., Achong, B. G., and Barr, Y. M. (1964). Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet* **1,** 702–703.

Fingeroth, J. D., Diamond, M. E., Sage, D. R., Hayman, J., and Yates, J. L. (1999). CD21-dependent infection of an epithelial cell line, 293, by Epstein–Barr virus. *J. Virol.* **73**(3), 2115–2125.

Forghani, B., Ni, L., and Grose, C. (1994). Neutralization epitope of the varicella-zoster virus gH:gL glycoprotein complex. *Virology* **199,** 458–462.

Forrester, A., Farrell, H., Wilkinson, G., Kaye, J., Davis, P. N., and Minson, T. (1992). Construction and properties of a mutant of herpes simplex virus type 1 with glycoprotein H coding sequences deleted. *J. Virol.* **66**(1), 341–348.

Fuller, A. O., Santos, R. E., and Spear, P. G. (1989). Neutralizing antibodies specific for glycoprotein H of herpes simplex virus permit viral attachment to cells but prevent penetration. *J. Virol.* **63**(8), 3435–3443.

Gan, Y. J., Chodosh, J., Morgan, A., and Sixbey, J. W. (1997). Epithelial cell polarization is a determinant in the infectious outcome of immunoglobulin A-mediated entry by Epstein–Barr virus. *J. Virol.* **71**(1), 519–526.

Gompels, U., and Minson, A. (1986). The properties and sequence of glycoprotein H of herpes simplex virus type 1. *Virology* **153,** 230–247.

Haan, K. M., Kwok, W. W., Longnecker, R., and Speck, P. (2000). Epstein–Barr virus entry utilizing HLA-DP or DQ as cofactors. *J. Virol.* **74**(5), 2451–2454.

Haan, K. M., and Longnecker, R. (2000). Coreceptor restriction within the HLA-DQ locus for Epstein–Barr virus infection. *Proc. Natl. Acad. Sci. USA* **97**(16), 9252–9257.

Haddad, R. S., and Hutt-Fletcher, L. M. (1989). Depletion of glycoprotein gp85 from virosomes made with Epstein–Barr virus proteins abolishes their ability to fuse with virus receptor-bearing cells. *J. Virol.* **63**(12), 4998–5005.

Heineman, T., Gong, M., Sample, J., and Kieff, E. (1988). Identification of the Epstein–Barr virus gp85 gene. *J. Virol.* **62**(4), 1101–1107.

Hutchinson, L., Browne, H., Wargent, V., Davis, P. N., Primorac, S., Goldsmith, K., Minson, A. C., and Johnson, D. C. (1992). A novel herpes simplex virus glycoprotein, gL, forms a complex with glycoprotein H (gH) and affects normal folding and surface expression of gH. *J. Virol.* **66**(4), 2240–2250.

Imai, S., Nishikawa, J., and Takada, K. (1998). Cell-to-cell contact as an efficient mode of Epstein–Barr virus infection of diverse human epithelial cells. *J. Virol.* **72**(5), 4371–4378.

Kaye, J. F., Gompels, U. A., and Minson, A. C. (1992). Glycoprotein H of human cytomegalovirus (HCMV) forms a stable complex with the HCMV UL115 gene product. *J. Gen. Virol.* **73**(Pt. 10), 2693–2698.

Kieff, E. (1996). Epstein Barr virus and its replication. *In* "Fields Virology" (B. Fields, D. Knipe, P. Howley, *et al.,* Eds.), Vol. 2, pp. 2343–2396. Lippincott–Raven, Philadelphia, PA.

Koizumi, S., Zhang, X. K., Imai, S., Sugiura, M., Usui, N., and Osato, T. (1992). Infection of the HTLV-I-harbouring T-lymphoblastoid line MT-2 by Epstein–Barr virus. *Virology* **188,** 859–863.

Labrecque, L. G., Barnes, D. M., Fentiman, I. S., and Griffin, B. E. (1995). Epstein–Barr virus in epithelial cell tumors: A breast cancer study. *Cancer Res.* **55**(1), 39–45.

Li, Q., Turk, S. M., and Hutt-Fletcher, L. M. (1995). The Epstein–Barr virus (EBV) BZLF2 gene product associates with the gH and gL homologs of EBV and carries an epitope critical to infection of B cells but not of epithelial cells. *J. Virol.* **69**(7), 3987–3994.

Li, Q. X., Young, L. S., Niedobitek, G., Dawson, C. W., Birkenbach, M., Wang, F., and Rickinson, A. B. (1992). Epstein–Barr virus infection and replication in a human epithelial cell system. *Nature* **356**(6367), 347–350.

Liu, D. X., Gompels, U. A., Nicholas, J., and Lelliott, C. (1993). Identification and expression of the human herpesvirus 6 glycoprotein H and interaction with an accessory 40K glycoprotein. *J. Gen. Virol.* **74**(Pt. 9), 1847–1857.

Miller, N., and Hutt-Fletcher, L. M. (1988). A monoclonal antibody to glycoprotein gp85 inhibits fusion but not attachment of Epstein–Barr virus. *J. Virol.* **62**(7), 2366–2372.

Molesworth, S. J., Lake, C. M., Borza, C. M., Turk, S. M., and Hutt-Fletcher, L. M. (2000). Epstein–Barr virus gH is essential for penetration of B cells but also plays a role in attachment of virus to epithelial cells. *J. Virol.* **74,** 6324–6332.

Nemerow, G. R., Wolfert, R., McNaughton, M. E., and Cooper, N. R. (1985). Identification and characterization of the Epstein–Barr virus receptor on human B lymphocytes and its relationship to the C3d complement receptor (CR2). *J. Virol.* **55**(2), 347–351.

Oba, D. E., and Hutt-Fletcher, L. M. (1988). Induction of antibodies to the Epstein–Barr virus glycoprotein gp85 with a synthetic peptide corresponding to a sequence in the BXLF2 open reading frame. *J. Virol.* **62**(4), 1108–1114.

Osato, T., and Imai, S. (1996). Epstein–Barr virus and gastric carcinoma. *Semin. Cancer Biol.* **7**(4), 175–182.

Paterson, R. L., Kelleher, C., Amankonah, T. D., Streib, J. E., Xu, J. W., Jones, J. F., and Gelfand, E. W. (1995). Model of Epstein–Barr virus infection of human thymocytes: Expression of viral genome and impact on cellular receptor expression in the T-lymphoblastic cell line, HPB-ALL. *Blood* **85**(2), 456–464.

Peeters, B., de Wind, N., Broer, R., Gielkens, A., and Moormann, R. (1992). Glycoprotein H of pseudorabies virus is essential for entry and cell-to-cell spread of the virus. *J. Virol.* **66**(6), 3888–3892.

Reisert, P. S., Spiro, R. C., Townsend, P. L., Stanford, S. A., Sairenji, T., and Humphreys, R. E. (1985). Functional association of class II antigens with cell surface binding of Epstein–Barr virus. *J. Immunol.* **134**(6), 3776–3780.

Rickinson, A., and Kieff, E. (1996). Epstein–Barr virus. *In* "Fields Virology" (B. Fields, D. Knipe, P. Howley, R. Chanock, J. Melnick, T. Monath, B. Roizman, and S. Straus, Eds.), Vol. 2, 3rd ed., pp. 2397–2446. Lippincott–Raven, Philadelphia, PA.

Roop, C., Hutchinson, L., and Johnson, D. C. (1993). A mutant herpes simplex virus type 1 unable to express glycoprotein L cannot enter cells, and its particles lack glycoprotein H. *J. Virol.* **67**(4), 2285–2297.

Shimizu, N., Yoshiyama, H., and Takada, K. (1996). Clonal propagation of Epstein–Barr virus (EBV) recombinants in EBV-negative Akata cells. *J. Virol.* **70**(10), 7260–7263.

Sixbey, J. W., and Yao, Q. Y. (1992). Immunoglobulin A-induced shift of Epstein–Barr virus tissue tropism. *Science* **255**(5051), 1578–1580.

Spaete, R. R., Perot, K., Scott, P. I., Nelson, J. A., Stinski, M. F., and Pachl, C. (1993). Coexpression of truncated human cytomegalovirus gH with the UL115 gene product or the truncated human fibroblast growth factor receptor results in transport of gH to the cell surface. *Virology* **193,** 853–861.

Spear, P. G., Eisenberg, R. J., and Cohen, G. H. (2000). Three classes of cell surface receptors for alphaherpesvirus entry. *Virology,* in press.

Speck, P., Kline, K. A., Cheresh, P., and Longnecker, R. (1999). Epstein–Barr virus lacking latent membrane protein 2 immortalizes B cells

with efficiency indistinguishable from wild-type virus. *J. Gen. Virol.* **80,** 2193.

Speck, P., and Longnecker, R. (1999). Epstein–Barr virus (EBV) infection visualized by EGFP expression demonstrates dependence on known mediators of EBV entry. *Arch. Virol.* **144**(6), 1123–1137.

Speck, P., and Longnecker, R. (2000). Epstein–Barr virus infects breast epithelial cells by cell-to-cell contact. *J. Natl. Cancer Inst.,* in press.

Wang, X., and Hutt-Fletcher, L. M. (1998). Epstein–Barr virus lacking glycoprotein gp42 can bind to B cells but is not able to infect. *J. Virol.* **72**(1), 158–163.

Wang, X., Kenyon, W. J., Li, Q., Mullberg, J., and Hutt-Fletcher, L. M. (1998). Epstein–Barr virus uses different complexes of glycoproteins gH and gL to infect B lymphocytes and epithelial cells. *J. Virol.* **72**(7), 5552–5558.

Yaswen, L. R., Stephens, E. B., Davenport, L. C., and Hutt Fletcher, L. M. (1993). Epstein–Barr virus glycoprotein gp85 associates with the BKRF2 gene product and is incompletely processed as a recombinant protein. *Virology* **195,** 387–396.

Yoshiyama, H., Imai, S., Shimizu, N., and Takada, K. (1997). Epstein–Barr virus infection of human gastric carcinoma cells: Implication of the existence of a new virus receptor different from CD21. *J. Virol.* **71**(7), 5688–5691.